Multiple myeloma partners

By Joanne Kotz, Senior Editor

The Institute of Cancer Research and **Cancer Research Technology Ltd.** are collaborating with Janssen Research & Development of **Johnson & Johnson** to modulate the unfolded protein response in multiple myeloma. Although no particulars have been disclosed by the partners, previous results from the U.K. team have suggested the kinase domain of IRE1 as a potential target in the pathway.

CRT is the commercial arm of **Cancer Research UK** (CRUK), a cancer charity that funds research, including at the ICR.

Standard of care for multiple myeloma (MM) includes the immunomodulatory drugs Thalomid thalidomide and Revlimid lenalidomide from **Celgene Corp.** and the proteasome inhibitor Velcade bortezomib from **Takeda Pharmaceutical Co. Ltd.** and partner J&J.

"We've made a lot of progress in multiple myeloma over the last decade, with notable increases in survival due to some highly active new drugs. But multiple myeloma is still largely an incurable disease. Patients need new treatments with less toxicity and that can provide further improvements in survival, which currently averages six to seven years from diagnosis," said Peter Lebowitz, global oncology therapeutic area head in the Janssen R&D unit.

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—Peter Lebowitz, Johnson & Johnson

Building up stress

The ICR-CRT-Janssen partnership will focus on an undisclosed target in a part of the stress response pathway called the unfolded protein response (UPR).

In tumors, environmental stresses such as hypoxia or nutrient deprivation can cause unfolded proteins to accumulate in the endoplasmic reticulum.

To cope with this stress, cancer cells initiate a UPR in which autophosphorylation of IRE1 (endoplasmic reticulum to nucleus signaling 1; ERN1) kinase domain activates the IRE1 ribonuclease domain. IRE1 then splices the x-box binding protein 1 (XBP1) mRNA, leading to the production of XBP1 protein, a transcription factor that induces the expression of UPR genes. Although this stress response pathway is activated in many tumors, MM is especially dependent on it.

According to Paul Workman, the ICR-CRT deal with Janssen is milestone and royalty driven, with the "expectation of getting to a clinical candidate."

Workman is deputy chief executive at the ICR, head of ICR's Division of Cancer Therapeutics and director of the CRUK Cancer Therapeutics Unit.

"What Janssen gets is access not only to our innovative, cancer-focused drug discovery but also our strong basic and translational multiple myeloma research. We get access to a bigger chemical deck, Janssen's pharmaceutical expertise and funding to move faster," said Workman. He added that both parties were independently interested in the target.

The ICR group will be led by Faith Davies, head of the myeloma targeted treatment team, and Ian Collins, head of a medicinal chemistry team in the CRUK Cancer Therapeutics Unit. The ICR researchers will work with a team at Janssen for a combined total of up to 25 scientists.

In 2011, a study co-led by Davies and coauthored by Collins reported that inhibiting the IRE1 kinase domain with a broad-spectrum kinase inhibitor reduced both *XBP1* mRNA splicing and XBP1 protein levels in MM cell lines.

These results established the IRE1 kinase domain as a potential target in the UPR pathway[1,2]—the ICR-Janssen group has not disclosed whether it will be pursuing this or another target.

Indeed, the IRE1 kinase domain is not the only route to disrupting the UPR. At least two companies—**MannKind Corp.** and **Ruga Corp.**—have preclinical programs targeting the ribonuclease domain of IRE1 in MM.

Independent of the Janssen collaboration, the ICR team is focusing on additional stress pathway targets. "We're working on Hsp70 and the HSF1 pathway and have identified early inhibitors," said Workman.

Heat shock protein 70 (Hsp70) and heat shock transcription factor 1 (HSF1) promote protein folding in response to heat shock and other stresses.

Workman said inhibitors of those targets could have broad antitumor activity. However, the team is planning to focus on a handful of indications, including MM and breast cancer.

Translocation SET up

The UPR is not the only emerging pathway in MM being tackled by ICR and CRT. The Janssen deal comes on the heels of an ICR-CRT partnership with **Astex Pharmaceuticals Inc.** around an epigenetic target—the histone methyltransferase Wolf-Hirschhorn syndrome candidate 1 (WHSC1; MMSET)—that is implicated in MM. About 20% of patients with MM have a tumor translocation that deregulates MMSET.

Workman said there is good validation for MMSET as an MM target. "The translocation leads to high MMSET expression and is prognostic for overall survival. Also, if you knock down MMSET you selectively kill MM cells that have the translocation."

The histone methyltranferase's activity appears to be important for the oncogenic effect of the translocation, suggesting that an MMSET inhibitor might have efficacy in these patients.

Workman noted that MMSET inhibitors might also have efficacy outside of MM. For instance, he cited a 2013 paper showing that MMSET functions downstream of enhancer of zeste homolog 2 (EZH2)—another histone methyltransferase that is widely implicated in cancer.[3]

"Hitting MMSET is also a way of tackling that pathway and potentially broadens the therapeutic context beyond multiple myeloma," he said.

In targeting MMSET, Astex is applying its fragment-based drug discovery platform, while in parallel the ICR is running high throughput screens. "The two approaches are different and complementary," said Astex president and director Harren Jhoti. "We're always very aware of what we are good at and also our limitations. We believe we have a strong technology for discovering drug candidates with our fragment-based platform, particularly for finding compounds against targets that are more difficult to drug—such as many epigenetic targets including MMSET."

The ICR team will do the "heavy lifting in biological testing and target validation," added Jhoti.

The goal is for an integrated ICR-Astex research team to identify a clinical candidate over the next several years. At that stage, the compound can be licensed to a pharma or taken through initial clinical testing at the ICR, said Jhoti.

"Astex will take the lead in evaluating opportunities to partner assets coming out of this program," he said.

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2. Kotz, J. *SciBX* **4**(10); doi:10.1038/scibx.2011.270
3. Asangani, I.A. *et al. Mol. Cell* **49**, 80–93 (2013)

COMPANIES AND INSTITUTIONS MENTIONED

Astex Pharmaceuticals Inc. (NASDAQ:ASTX), Dublin, Calif.
Cancer Research Technology Ltd., London, U.K.
Cancer Research UK, London, U.K.
Celgene Corp. (NASDAQ:CELG), Summit, N.J.
The Institute of Cancer Research, Sutton, U.K.
Johnson & Johnson, (NYSE:JNJ), New Brunswick, N.J.
MannKind Corp. (NASDAQ:MNKD), Valencia, Calif.
Ruga Corp., Palo Alto, Calif.
Takeda Pharmaceutical Co. Ltd. (Tokyo:4502), Osaka, Japan